Hypoxia-specific Production of Exosomes from iPSC-derivatives for Myocardial Repair

Grant Award Details

Hypoxia-specific Production of Exosomes from iPSC-derivatives for Myocardial Repair

Grant Type: Quest - Discovery Stage Research Projects

Grant Number: DISC2-12540

Project Objective: To identify best candidate for induction of cardiomyocyte proliferation for self-repair of the injured myocardium, selecting from (i) exosomes (hEx) generated from hypoxia-injured human iPSC-derived cardiomyocytes (iCMs), (ii) miR20/92, and (iii) siNotch3. Nanoparticle delivery formulation will encapsulate hEx, miRs and siRNA to prevent immunologic reaction following intramyocardial injection.

Investigator:

Name:	Phillip Yang
Institution:	Stanford University
Type:	PI

Disease Focus: Heart Disease, Heart failure

Human Stem Cell Use: iPS Cell

Award Value: $1,418,023

Status: Active

Grant Application Details

Application Title: Hypoxia-specific Production of Exosomes from iPSC-derivatives for Myocardial Repair

Public Abstract:

Research Objective

A lead therapeutic candidate will be selected: 1) exosomes from hypoxia-injured iPSC-derived cardiomyocytes (iCMs), 2) exosomal miRNA cluster, and 3) siRNA inhibition of exosomal target gene, Notch3.

Impact

Effective targeted therapy to restore the injured and vulnerable myocardium is urgently needed to reduce the high mortality of HF patients. Promising discovery of iPSC biology will restore the heart.

Major Proposed Activities

- Patient-specific iCMs are generated from 4 heart failure (HF) patients (2 white and 2 under-represented minority). Exosomes are generated from their hypoxia-injured iCMs to compare their efficacy.
- The proliferative and reparative effects of hEx1-4, hEx molecular cargo, miR20b/92a, and hEx molecular target, Notch3, are compared, using hypoxia-injury model of iCMs from a normal subject.
- The therapeutic efficacy of the 2 leading hEx determined above, miR20b/92a, and siNotch3 will be compared in porcine HF model. Cardiomyocyte proliferation and myocardial restoration will be confirmed.
- A leading candidate will be identified. Dose-dependent myocardial restoration will determine the optimal balance between cardiomyocyte proliferation and electromechanical stability of the heart.
- Pre-pre-IND FDA meeting will be held at Month 22.

Statement of Benefit to California:

In California, heart failure (HF) is the leading cause of hospital admission and a major public health epidemic. Despite significant therapeutic advances over the last 3 decades, 5-year survival is a dismal 50% today. Furthermore, racial disparity is observed in the care of HF patients. Ischemic injury is the primary etiology of HF. Restoration of the heart by proliferating the cardiomyocytes to repair the injury will transform our therapeutic approach and address a critical unmet need in HF.

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